DOI: 10.1002/adsc.200700211

A Practical Transition Metal-Free Aryl-Aryl Coupling Method: Arynes as Key Intermediates

Frédéric R. Leroux,[a,*] Laurence Bonnafoux,[a] Christophe Heiss,[a] Françoise Colobert,[a] and Don Antoine Lanfranchi[a]

[a] Laboratoire de stéréochimie, Université Louis Pasteur (ECPM), CNRS, 25 rue Becquerel, 67087 Strasbourg Cedex 2, France
Fax: (+33)-(0)3-9024-2742; e-mail: frederic.leroux@ecpm.u-strasbg.fr

Received: April 26, 2007; Revised: August 13, 2007; Published online: October 4, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Upon treatment of various aryllithium intermediates with 1,2-dibromobenzene or 1-bromo-2-iodobenzene, dissymmetrical *ortho,ortho'*-di-, tri- and even tetrasubstituted bromo- or iodobiaryls become readily available. The crucial steps in all these reactions were the nucleophilic addition of the organolithium precursor to a transient aryne species released from it by β-elimination of a lithium halide and, stabilization of the resulting 2-biaryllithium intermediate by *in situ* transfer of bromine or iodine from the starting material. This straightforward transition metal-free access to biaryls allows the preparation of highly valuable halobiaryls on a gram scale in excellent yields. These precursors can be subsequently functionalized by highly regioselective halogen/metal permutations into a vast variety of target molecules. This was demonstrated in the synthesis of several mono- and diphosphine ligands.

Keywords: arynes; biaryls; C–C coupling; halogen/metal exchange; phosphines

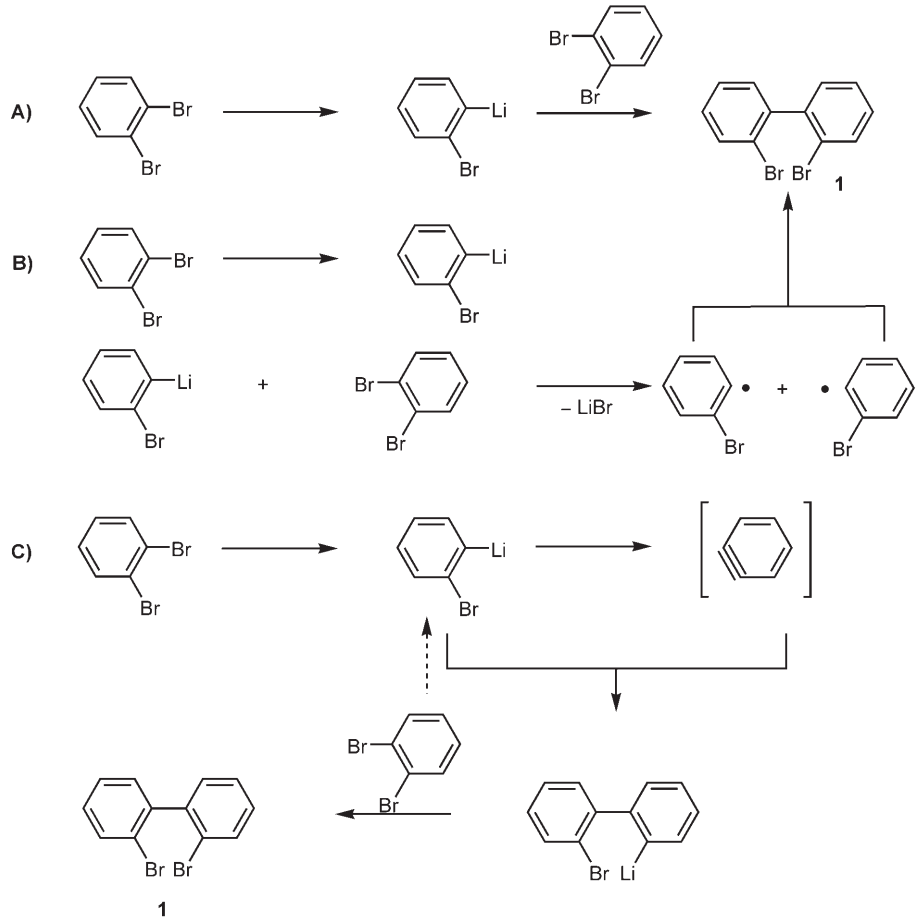
Introduction

Axially chiral, *ortho*-functionalized biaryls are attracting more and more attention. One reason is the growing number of biologically active natural products which contain the biaryl motif (for example, vancomycin, steganone, and michellamine).[1–6] Furthermore, the stereogenic axes provide rigid molecular frameworks for highly efficient tools in asymmetric synthesis,[7–11] among them chiral ligands like BINAP[12] and MeO-BIPHEP[13] just to mention two of the most prominent ones. The biaryl core is also commonly encountered in the liquid crystal field, where derivatives have found commercial applications.[14,15] Moreover, the biphenyl unit belongs to the six or seven privileged structures[16–20] reputed to be "safe bets" in pharmaceutical research, as they ascertain versatility and high hit rates. The preparation of these biaryls often relies on the classical cross-coupling processes such as Suzuki–Miyaura, Negishi, Kumada–Tamao–Corriu, Stille or Ullmann coupling.[21,22] The limitation of these reactions is often the preparation of the coupling partners, i.e., the corresponding aryl electrophiles and aryl nucleophiles. In contrast, the functionalization of *ortho*-bromobiaryls by halogen/metal interconversion and subsequent reaction with various electrophiles offers many synthetic advantages.[23–26] However, the synthesis of the *ortho*-halobiaryl intermediates is not often straightforward. In 1957, Gilman[27] and later Lau and co-workers[28] reported the reaction of 1,2-dibromobenzene with half a molar equivalent of butyllithium in THF at −78 °C affording 2,2′-dibromobiphenyl (**1**, Scheme 1). These results, together with our previous work[29] prompted us to investigate the scope and limitations of this highly efficient non-catalyzed carbon-carbon coupling towards *ortho*-bromobiaryls having new and uncommon structural patterns.

Results and Discussion

The butyllithium-promoted formation of 2,2′-dibromobiphenyl (**1**) can be explained by three possible mechanisms. First, an intermediate *o*-bromophenyllithium attacks 1,2-dibromobenzene in a kind of S_NAr mechanism (Scheme 1, **A**). This hypothesis was first described by Gilman and coworkers[27] in the late 1950s. However, such a mechanistic pattern of a standard nucleophilic addition/nucleofugal elimination mode is restricted to heavily strained[30] or acceptor-activated[31–33] haloarenes as substrates. Therefore, this kind of mechanism can be ruled out.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Possible pathways for the butyllithium promoted formation of 2,2′-dibromobiphenyl (**1**).

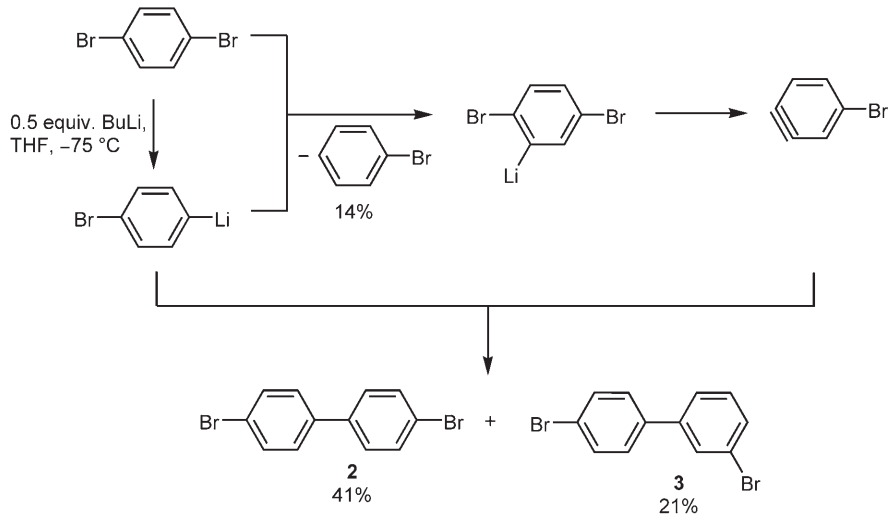
Alternatively, the reaction could proceed through a biradical formation and recombination due to the high propensity of electron-rich aryllithiums to act as electron donors (Scheme 1, **B**).[34] Wagner and Mioskowski could disqualify the "electron transfer" pathways by performing the coupling reaction in the absence of light and in the presence of radical scavengers like TEMPO.[34–36]

An alternative mechanism is based on the intermediacy of 1,2-didehydrobenzene (1,3-cyclohexadien-5-yne, benzyne, Scheme 1, **C**). Here, the crucial steps are, first the nucleophilic addition of the organolithium precursor to the transient aryne species released from it by β-elimination of a lithium halide and, second, stabilization of the resulting 2-biaryllithium intermediate by *in situ* transfer of bromine.

It has been shown that the reaction of aryl halides with strong bases involves the intermediate formation of arynes.[37] Aryne formation occurs *via* a two-step process. Proton abstraction generates the *ortho*-haloaryl carbanion which subsequently eliminates halide to form the aryne. The aryne can then undergo nucleophilic attack at either side to yield product carbanions.[38]

We could experimentally confirm this pathway by treating 1,4-dibromobenzene with half an equivalent of butyllithium. The S_NAr mechanism as well as the $S_{RN}1$ pathway would only afford 4,4′-dibromobiphenyl (**2**) as reported by Gilman.[27] However, we were able to show by careful gas chromatographic analysis that 4,4′-dibromobiphenyl (**2**) (41%) and its 3,4′-isomer **3** (21%) were formed concomitantly with bromobenzene (14%; Scheme 2). These findings are only in agreement with a metallation, elimination, addition sequence featuring 4-bromophenyllithium, 2,5-dibromophenyllithium, and 4-bromo-1,2-didehydrobenzene as transient entities. In fact, 1,4-dibromobenzene undergoes an *ortho*-metallation with 1-bromo-4-lithiobenzene as base affording 1,4-dibromo-2-lithiobenzene and bromobenzene. Subsequent lithium bromide elimination leads to 4-bromo-1,2-didehydrobenzene which in turn adds 4-bromophenyllithium as a nucleophile at the 3- and 4-positions yielding 4,4′- and 3,4′-dibromobiphenyl, respectively.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Experimental evidence for an aryne intermediate.

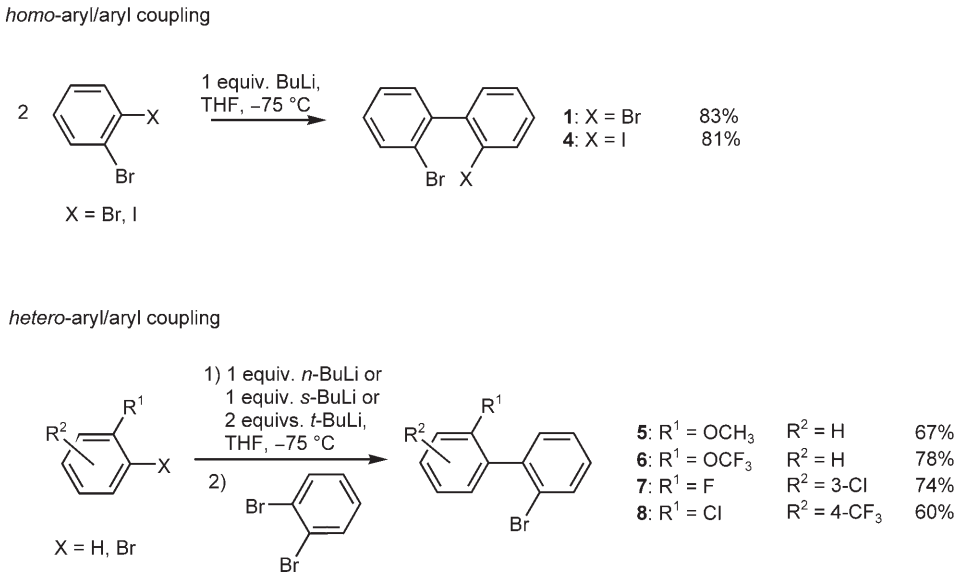
Based on these findings, we decided to investigate the scope and limitations in the synthesis of di-, tri- and tetrasubstituted biaryls.

ortho,ortho′-Disubstituted Biaryls

When 1-bromo-2-iodobenzene is used as the starting material instead of 1,2-dibromobenzene, iodine transfer takes place after treatment with half a molar equivalent of butyllithium and 2-bromo-2′-iodobiphenyl (**4**) is obtained in a yield of 81%. This access can be described as a *homo*-aryl/aryl coupling between two identical aryllithium species (Scheme 3).

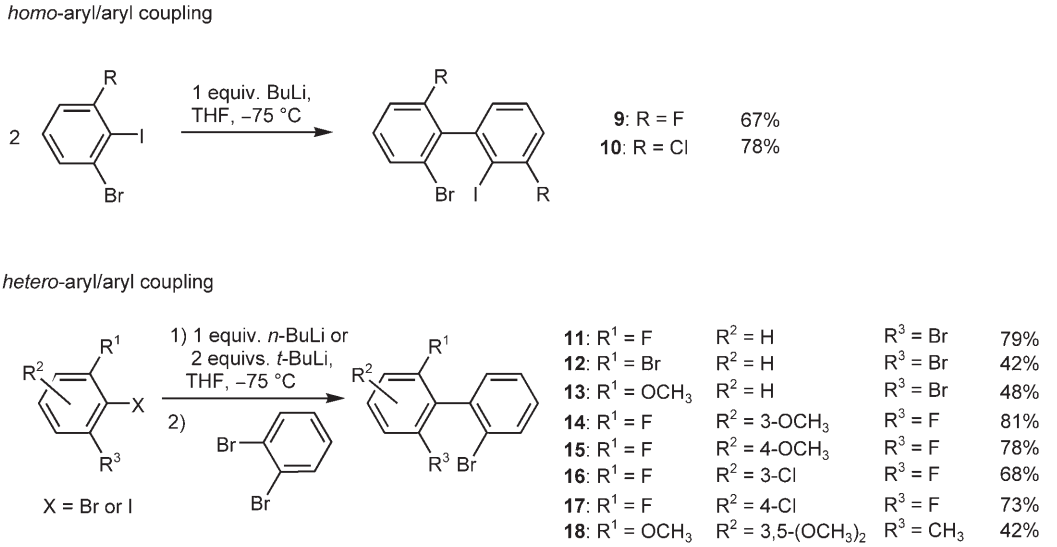
The aryl-aryl coupling can be modified by generating the aryne from a thermally labile 2-haloaryllithium species in the presence of a more stable aryllithium compound which will then act as trapping reagent. In fact, 2-bromophenyllithium formed by halogen/metal permutation from 1,2-dibromobenzene is labile at temperatures above −125 °C and does not survive under the experimental conditions but instantaneously eliminates lithium bromide releasing benzyne. The latter can then be trapped by the thermally less sensitive aryllithium component. Under these reaction conditions, a *hetero*-aryl/aryl coupling between two different aryl units can be achieved (Scheme 3).

When a solution of 2-bromoanisole was treated with two equivalents of *tert*-butyllithium, the corre-



Scheme 3. Synthesis of *ortho,ortho′*-disubstituted biaryls by *homo*- and *hetero*-aryl/aryl coupling.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 4. Synthesis of *ortho,ortho′*-trisubstituted biaryls by *homo*- and *hetero*-aryl/aryl coupling.

sponding 2-anisyllithium reacts with 1,2-dibromobenzene affording 2-bromo-2′-methoxybiphenyl (**5**) in 67% yield. The aryllithium intermediate, if not obtained by halogen/metal exchange,[24] can be generated by metallation[25,39] only if the metallating agent is an organolithium base. Trifluoromethoxybenzene was metallated with *sec*-butyllithium in THF at −75 °C followed by the addition of 1,2-dibromobenzene. The biphenyl **6** was obtained in a yield of 78%. Analogously 1-chloro-2-fluorobenzene gave the biphenyl **7** (74%) and 3-chlorobenzotrifluoride the corresponding derivative **8** in a yield of 60%, respectively (Scheme 3).

ortho,ortho′-Trisubstituted Biaryls

Next, we decided to investigate if trisubstituted biaryls will be accessible by this approach. In fact, 1-bromo-3-fluoro-2-iodobenzene could be easily converted by *homo*-aryl/aryl coupling of the intermediate 2-bromo-6-fluorophenyllithium into 2-bromo-3′,6-difluoro-2′-iodobiphenyl (**9**; 67%), and 1-bromo-3-chloro-2-iodobenzene into 2-bromo-3′,6-dichloro-2′-iodobiphenyl, respectively (**10**; 78%; Scheme 4).

In contrast, when 2-bromo-6-fluorophenyllithium was treated with one equivalent of 1,2-dibromobenzene at −75 °C, 2,2′-dibromo-6-fluorobiphenyl (**11**) was obtained in 79% yield by *hetero*-aryl/aryl coupling. As depicted in Scheme 4, various 2,2′,6-trisubstituted biphenyl derivatives (**11**–**18**) could be prepared analogously by this approach.

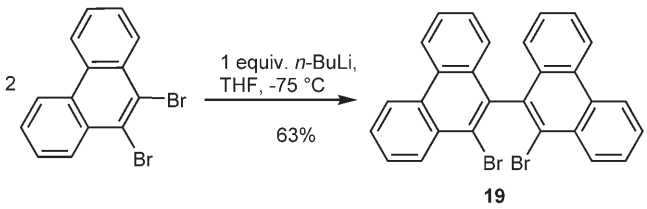
In all these transformations, a clean formation of the aryllithium intermediate (either by halogen/metal exchange or by metallation with an alkyllithium base) is absolutely crucial. For example, the direct metallation of 1-bromo-3-fluorobenzene with LDA or LTMP generates the aryllithium intermediate very easily. However, the latter does not react in a clean way with released benzyne. Indeed, under the reaction conditions, diisopropylamine adds as a nucleophile to the *in situ* generated benzyne, leading to undesired side-products. Therefore, one has to prepare first the corresponding aryl iodide by metallation with an amide base like LDA followed by trapping with iodine. The iodo precursor can then be submitted to an iodine/lithium exchange in order to generate an aryllithium intermediate without the presence of amines.

ortho,ortho′-Tetrasubstituted Biaryls

To the best of our knowledge, all methods affording *ortho,ortho′*-tetrasubstituted biaryls are based on transition metal catalysis (like the copper-catalyzed Ullman coupling) and/or require suitable ligands (like in the palladium-catalyzed Suzuki–Miyaura coupling reaction). In order to investigate the scope and limitations of the transition metal-free aryne coupling, we decided to treat 9,10-dibromophenanthrene with half an equivalent of butyllithium. The desired *ortho,ortho′*-tetrasubstituted biphenyl, 10,10′-dibromo-9,9′-bisphenanthryl (**19**), was obtained in a good yield of 63% (Scheme 5), underlining the great synthetic value of this coupling procedure.

So far, 1,2-dibromobenzene or 1-bromo-2-iodobenzene were used as aryne source and the aryllithium part was subsequently modified. Therefore we investigated if the aryne precursor could also be modified. When 1,3-dimethoxybenzene was submitted to an *ortho*-metallation and the resulting 2-lithio-1,3-dimethoxybenzene was treated with 1,2-dibromo-4,5-dime-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 5. Synthesis of an *ortho,ortho'*-tetrasubstituted biaryl by *homo*-aryl/aryl coupling.

thoxybenzene (1,2-dibromoveratrole) as "aryne source". In this way, we obtained smoothly in a yield of 55% the highly electron-rich biphenyl **20** (Scheme 6).

Synthesis of Phosphine Ligands

Diphosphines supported on stereogenic atropoisomeric biaryl scaffolds like BINAP and MeO-BIPHEP, became very efficient chiral inductors in most stereoselective reactions. Dialkylarylphosphine ligands are highly efficient ligands for the Suzuki–Miyaura couplings of aryl chlorides. As we could show very recently, the use of *ortho*-bromobiaryls allows the straightforward synthesis of biaryl mono- and diphosphine ligands in a modular way by means of highly selective halogen/metal exchange reactions.[40,41] Thus, the synthesis of these *ortho*-bromobiaryls by means of aryne coupling allows the synthesis of new ligands as shown in Scheme 7.

For example 2,2′-dibromo-6-methoxy-biphenyl (**13**) could be readily converted into 2,2′-bis(dicyclohexylphosphine)-6-methoxybiphenyl (**21**; 74%) by double bromine/lithium exchange followed by trapping with two equivalents of chlorodicyclohexylphosphine. In a similar way the monophosphines **22** and **23** were obtained after bromine/lithium exchange and subsequent trapping of the biphenylyllithium with chlorodicyclohexylphosphine in a yield of 87% and 81%, respectively. 2,2′-Bis(dicyclohexylphosphino)-6-fluorobiphenyl (**24**) was prepared in 79% yield by consecutive treatment of 2,2′-dibromo-6-fluorobiphenyl (**11**) with butyllithium and chlorodicyclohexylphosphine (Scheme 7). However, the electron-rich biaryl **20** afforded the desired monophosphine **25** only in a very poor yield of 7%. The yield could not be improved by modification of the organolithium base, the solvent or reaction time.

All phosphines **21**–**25** were synthesized starting from mono- or dibromobiaryl intermediates after halogen/metal exchange and trapping with the appropriate chlorophosphine during the last step of the synthesis. In most cases, the corresponding mono- or diphosphines are obtained in excellent yields.

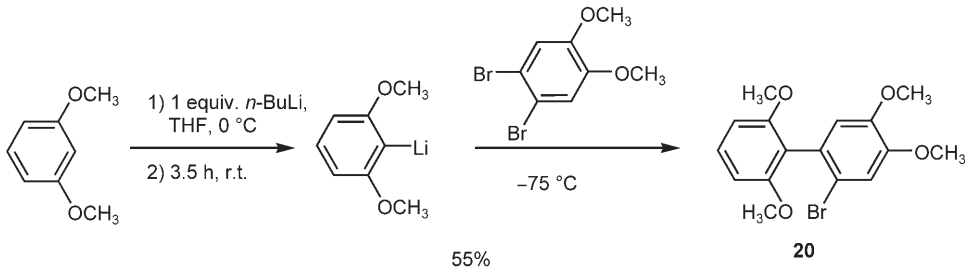
Conclusions

In conclusion, we have developed a simple and inexpensive method for the synthesis of dissymmetrically substituted *ortho*-bromobiaryl building blocks that are valuable intermediates toward complex *ortho*-substituted biaryl structures. This methodology employs the formation of a thermodynamically stable aryllithium intermediate *via* halogen/metal exchange or metallation and its subsequent reaction with 1,2-dibromobenzene. Experimental details confirm without any doubt the transient formation of a high-energy species, a 1,2-didehydrobenzene adding a stabilized aryllithium derivative. The compounds can be prepared on a gram scale without any difficulties and subsequently functionalized by means of regioselective halogen/metal permutations into important target molecules as exemplified in the synthesis of mono- and diphosphine ligands. Other classes of substrates are currently under investigation to expand the scope of this synthetically useful non-catalyzed reaction.

Experimental Section

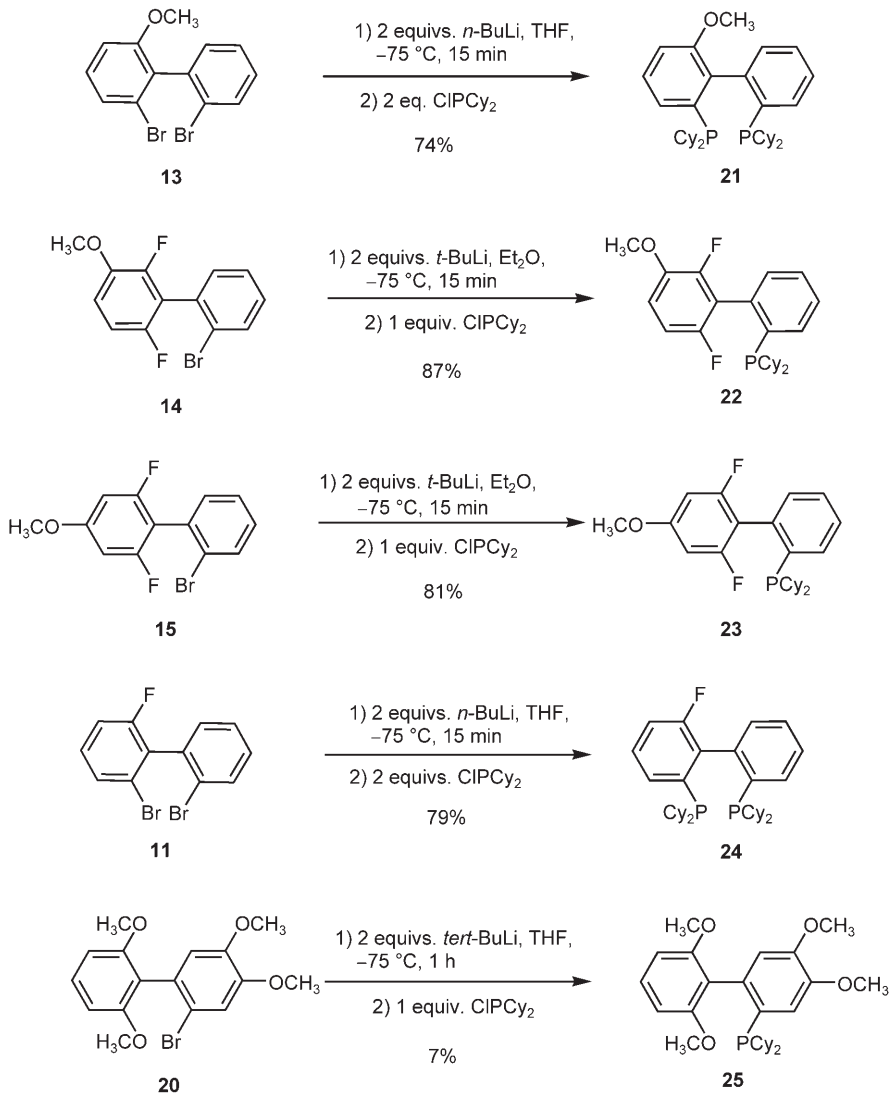
General Remarks

Starting materials, if commercial, were purchased and used as such, provided that adequate checks (melting ranges, refractive indices, and gas chromatography) had confirmed the claimed purity. When known compounds had to be prepared according to literature procedures, pertinent references are given. Air- and moisture-sensitive materials were stored in



Scheme 6. Aryne coupling using 1,2-dibromoveratrole as aryne source.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 7. Synthesis of C_1-symmetric biarylmono- and diphosphines.

Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of argon, using appropriate glassware. Diethyl ether and tetrahydrofuran were dried by distillation from sodium after the characteristic blue color of sodium diphenyl ketyl (benzophenone-sodium "radical-anion") had been found to persist.[42,43] Ethereal or other organic extracts were dried by washing with brine and then by storage over sodium sulfate. If no reduced pressure is specified, boiling ranges (b.p.) refer to ordinary atmosphere conditions (725±25 Torr). Melting ranges (mp) given were found to be reproducible after recrystallization, unless stated otherwise ("dec."), and were corrected using a calibration curve established with authentic standards. If melting points are missing, it means all attempts to crystallize the liquid at temperatures down to −75 °C failed. The temperature of dry ice/acetone baths is consistently indicated as −75 °C and "room temperature" (22–26 °C) as 25 °C. Silica gel (Merck Silica Gel 60, 40–63 μm) was used for column chromatography. The solid support was suspended in hexanes and, when all air bubbles had escaped, was washed into the column. When the level of the liquid was still 3–5 cm above the support layer, the dry powder, obtained by adsorption of the crude mixture to some 25 mL of silica and subsequent evaporation of the solvent, was poured on top of the column. ^{1}H and (^{1}H decoupled) ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400 or 300 and 101 or 75 MHz, respectively. Chemical shifts are reported in δ units, parts per million (ppm) and were measured relative to the signals for residual chloroform (7.27 ppm). Coupling constants J are given in Hz. Coupling patterns are abbreviated as, for example, s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), td (triplet of doublets) and m (multiplet).

Starting Materials; 1-Bromo-3-fluoro-2-iodobenzene[29]

At −75 °C, butyllithium (0.10 mol) in hexanes (55 mL) and diisopropylamine (14 mL, 10 g, 0.10 mol) were added successively to tetrahydrofuran (0.20 L). After 15 min 3-bromofluorobenzene (11 mL, 18 g, 0.10 mol) was added. The mix-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ture was kept for 2 h at −75 °C before a solution of iodine (25 g, 0.10 mol) in tetrahydrofuran (50 mL) was added. After addition of a 10% aqueous solution (0.10 L) of sodium thiosulfate, the mixture was extracted with diethyl ether (3×0.10 L). The combined organic layers were dried over sodium sulfate before being evaporated to dryness. Distillation afforded the pure product; yield: 23.47 g (78%).

1-Bromo-3-chloro-2-iodobenzene:[29] Analogously to 1-bromo-3-fluoro-2-iodobenzene starting from 1-bromo-3-chlorobenzene (12 mL, 19 g, 0.10 mol). Upon crystallization from ethanol, colorless needles were obtained; yield: 27.29 g (86%).

1,3-Dibromo-2-iodobenzene:[29,40,41] Analogously to 1-bromo-3-fluoro-2-iodobenzene starting from 1,3-dibromobenzene (0.12 L, 0.24 kg, 1.0 mol). Upon crystallization from ethanol (1.0 L), colorless platelets were obtained; yield: 0.33 kg (91%).

1-Bromo-2-iodo-3-trifluoromethoxybenzene: At −75 °C, butyllithium (0.10 mol) in hexanes (55 mL) and diisopropylamine (14 mL, 10 g, 0.10 mol) were added successively to tetrahydrofuran (0.2 L). After 15 min 1-bromo-3-trifluoromethoxy-benzene (13 mL, 20 g, 0.10 mmol) was added. The mixture was kept for 2 h at −75 °C before a solution of iodine (25 g, 0.10 mol) in tetrahydrofuran (50 mL) was added. After addition of a 10% aqueous solution (0.10 L) of sodium thiosulfate the mixture was extracted with diethyl ether (3×0.10 L). The combined organic layers were dried over sodium sulfate before being evaporated to dryness. Distillation afforded the pure product; yield: 31.92 g (87%).

Disubstituted Biaryls by *Homo*-Aryl/Aryl Coupling; 2-Bromo-2′-iodobiphenyl (4)[29]

At −75 °C, butyllithium (50 mmol) in hexanes (31 mL) was added to a solution of 1-bromo-2-iodobenzene (13 mL, 28 g, 0.10 mol) in tetrahydrofuran (0.20 L). The mixture was then warmed to 25 °C over a two hours period and hydrolyzed with a 1.0 M aqueous hydrochloric acid solution (0.10 L). After separation of the phases, the aqueous layer was extracted with diethyl ether (3×0.20 L). The combined organic layers were dried over sodium sulfate before being evaporated to dryness. Upon crystallization from ethanol, colorless needles were obtained; yield: 14.54 g (81%).

Disubstituted Biaryls by *Hetero*-Aryl/Aryl Coupling; 2′-Bromo-2-methoxybiphenyl (5)

2-Bromoanisole (4.7 g, 25 mmol) was added to a −75 °C cold solution of *tert*-butyllithium (50 mmol) in pentanes (30 mL) and tetrahydrofuran (70 mL). After 5 min, the temperature was increased to −25 °C for 15 min. Then, a solution of 1,2-dibromobenzene (3.0 mL, 5.9 g, 25 mmol) in tetrahydrofuran (10 mL) was added dropwise, over a 10 min period. The mixture was allowed to reach room temperature before water (25 mL) was added followed by extraction with diethyl ether (3×20 mL). The combined organic layers were dried and evaporated. Column chromatography on silica gel (20 mL) using cyclohexane as eluent afforded **5**. Crystallization from ethanol gave colorless needles; yield: 4.41 g (67%).

2′-Bromo-2-trifluoromethoxybiphenyl (6): Trifluoromethoxybenzene (4.1 g, 25 mmol) was added to a −75 °C cold solution of *sec*-butyllithium (25 mmol) in cyclohexane (20 mL) and tetrahydrofuran (30 mL). After 2 h at −75 °C, a solution of 1,2-dibromobenzene (3.0 mL, 5.9 g, 25 mmol) in tetrahydrofuran (5.0 mL) was added as described in the preceding paragraph. The reaction mixture was washed with brine (3×20 mL) and extracted with diethyl ether (3×20 mL). Column chromatography on silica gel (100 mL) using cyclohexane as eluent afforded a colorless oil; yield: 6.18 g (78%).

2-Fluoro-3-chloro-2′-bromobiphenyl (7): Prepared analogously to biphenyl **6** starting from 1-chloro-2-fluorobenzene (3.3 g, 25 mmol) affording a colorless oil; yield: 5.28 g (74%).

2-Chloro-6-trifluoromethyl-2′-bromobiphenyl (8): Prepared analogously as biphenyl **6** starting from 1-chloro-3-trifluoromethylbenzene (1.8 g, 10 mmol) affording a colorless oil; yield: 2.01 g (60%).

Trisubstituted Biaryls by *Homo*-Aryl/Aryl Coupling; 2-Bromo-3′,6-difluoro-2′-iodobiphenyl (9)[29]

At −75 °C, butyllithium (13 mmol) in hexanes (7.0 mL) was added to a solution of 1-bromo-3-fluoro-2-iodo-benzene (7.5 g, 25 mmol) in tetrahydrofuran (50 mL). After 45 min the mixture was allowed to reach 25 °C over a two-hour period. Water (0.10 L) was added to the reaction mixture followed by extraction with diethyl ether (3×0.10 L). The combined organic layers were dried over sodium sulfate before being evaporated to dryness. Upon crystallization from ethanol, colorless needles were obtained; yield: 3.31 g (67%).

2-Bromo-3′,6-dichloro-2′-iodobiphenyl (10):[29] Prepared analogously as biphenyl **9** starting from 1-bromo-3-chloro-2-iodobenzene (16 g, 50 mmol); colorless needles; yield: 8.34 g (78%).

Trisubstituted Biaryls by *Hetero*-Aryl/Aryl Coupling; 2,2′-Dibromo-6-fluorobiphenyl (11)[29]

At −75 °C, butyllithium (50 mmol) in hexanes (24 mL) was added to a solution of 1-bromo-3-fluoro-2-iodo-benzene (7.5 g, 25 mmol) in tetrahydrofuran (50 mL). After 45 min 1,2-dibromobenzene (3.0 mL, 5.9 g, 25 mmol) was added to the mixture. After 2 h at −75 °C the mixture was allowed to obtain 25 °C over a two hours period. Water (0.10 L) was added to the reaction mixture followed by extraction with diethyl ether (3×0.10 L). Crystallization from ethanol afforded **11** as colorless needles; yield: 6.52 g (79%).

2,2′,6-Tribromobiphenyl (12):[29,40,41] Prepared analogously as biphenyl **11** starting from 1,3-dibromo-2-iodobenzene (9.0 g, 25 mmol). The residue was purified by flash chromatography which afforded **12** as colorless needles; yield: 4.10 g (42%).

2,2′-Dibromo-6-methoxybiphenyl (13):[40,41] At −100 °C, *tert*-butyllithium (25 mmol) in pentane (18 mL) was added to a solution of 3-bromo-2-iodoanisole[45] (3.91 g, 12.5 mmol) in tetrahydrofuran (50 mL). After 45 min 1,2-dibromobenzene (1.5 mL, 3.0 g, 12.5 mmol) was added to the mixture. After 2 h at −100 °C the mixture was allowed to obtain 25 °C over a twelve-hour period. Water (0.10 L) was added

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

to the reaction mixture followed by extraction with diethyl ether (3×0.10 L). After crystallization from ethanol 2,2′-dibromo-6-methoxybiphenyl (**13**) was obtained as colorless cubes; yield: 2.05 g (48%).

2,6-Difluoro-2′-bromo-3-methoxybiphenyl (14): At −75°C, 2,4-difluoroanisole (3.6 g, 25 mmol) was added to a solution of *sec*-butyllithium (25 mmol) in cyclohexane (15 mL) and tetrahydrofuran (35 mL). After 45 min, 1,2-dibromobenzene (3.0 mL, 5.9 g, 25 mmol) was added and the mixture was allowed to reach room temperature in the course of 12 h. Evaporation of the solvent followed by column chromatography on silica gel (100 mL) using cyclohexane as the eluent afforded **14** as colorless oil; yield: 6.06 g (81%).

2,6-Difluoro-2′-bromo-4-methoxybiphenyl (15): Prepared analogously as biphenyl **14** from 3,5-difluoroanisole (3.6 g, 25 mmol) affording colorless needles; yield: 5.83 g (78%).

2,6-Difluoro-3-chloro-2′-bromobiphenyl (16): Prepared analogously as biphenyl **14** from 1-chloro-2,4-difluorobenzene (1.5 g, 10 mmol) affording a colorless oil; yield: 2.06 g (68%).

2,6-Difluoro-4-chloro-2′-bromobiphenyl (17): Prepared analogously as biphenyl **14** from 1-chloro-3,5-difluorobenzene (1.5 g, 10 mmol) affording a colorless oil; yield: 2.22 g (73%).

2′-Bromo-3,5,6-trimethoxy-2-methylbiphenyl (18): Prepared analogously as biphenyl **11** starting from 3-bromo-1,2,5-trimethoxy-4-methylbenzene[46] (2.6 g, 10 mmol). The pure compound could be obtained by column chromatography on silica gel using ethyl acetate/cyclohexane (1:9) as eluent. Crystallization from ethyl acetate/hexanes (1:5) afforded **18** as colorless needles; yield: 1.4 g (42%).

Tetrasubstituted Biaryls by *Homo*-Aryl/Aryl Coupling; 10,10′-Dibromo-[9,9′]biphenanthrenyl (19)[29]

At −75°C, butyllithium (5.0 mmol) in hexanes (3.1 mL) was added to a solution of 9,10-dibromophenanthrene[47] (3.3 g, 10 mmol) in tetrahydrofuran (20 mL). The mixture was then warmed to 25°C over a two-hour period and hydrolyzed with a 1.0 M aqueous hydrochloric acid solution (0.10 L). After separation of the phases, the aqueous layer was extracted with dichloromethane (3×0.20 L). The combined organic layers were dried over sodium sulfate before being evaporated to dryness. Upon crystallization from ethanol, colorless needles were obtained; yield: 1.61 g (63%).

2-Bromo-4,5,2′,6′-tetramethoxybiphenyl (20): At 0°C, butyllithium (5.5 mmol), in hexanes (3.6 mL) was added dropwise to a solution of 1,3-dimethoxybenzene (5.5 mmol, 0.8 g, 0.7 mL) in tetrahydrofuran (13 mL). Immediately after complete addition, the solution was allowed to reach 25°C. After 3.5 h, the reaction mixture was cooled to −78°C and a solution of 1,2-dibromo-4,5-dimethoxybenzene[48] (5.0 mmol, 1.5 g) in tetrahydrofuran (2.5 mL) was added dropwise. The reaction mixture was allowed to reach 25°C during a twelve hours period. Water (10 mL) was added, followed by extraction with ethyl acetate (4×10 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated. The residue was purified by chromatography on silica gel and crystallization from methanol affording 2-bromo-4,5,2′,6′-tetramethoxybiphenyl (**20**) as colorless cubes; yield: 1.0 g (55%).

Synthesis of Mono- and Diphosphines; 2′,6-Bis(dicyclohexylphosphino)-2-methoxybiphenyl (21)[40,41]

At −75°C, butyllithium (0.10 mol) in hexanes (63 mL) was added to a solution of **13** (17 g, 50 mmol) in tetrahydrofuran (0.25 L). After 15 min at −75°C, the mixture was treated with a 2.0 M solution of chlorodicyclohexylphosphine (22 mL, 24 g, 0.10 mol) in toluene (50 mL). The mixture was allowed to reach 25°C and treated with a saturated aqueous solution of ammonium chloride (0.10 L). The mixture was extracted with ethyl acetate (3×50 mL), and the combined organic layers were dried over sodium sulfate. The diphosphine **21** was obtained after evaporation of the solvents and crystallization from methanol (0.10 L) as colorless cubes; yield: 43 g (74%).

2,6-Difluoro-3-methoxy-2′-dicyclohexylphosphinobiphenyl (22): Biphenyl **14** (1.5 g, 5.0 mmol) was added to a solution of *tert*-butyllithium (10 mmol) in pentanes (6.0 mL) and diethyl ether (15 mL) at −75°C. After 15 min at −75°C, a solution of chlorodicyclohexylphosphine (1.0 mL, 1.0 g, 5.0 mmol) in tetrahydrofuran (5.0 mL) was added to the reaction mixture. Evaporation of the solvent followed by column chromatography on silica gel (100 mL) using cyclohexane as the eluent gave a colorless oil. Crystallization from methanol afforded colorless needles; yield: 1.83 g (87%).

2,6-Difluoro-4-methoxy-2′-dicyclohexylphosphino-biphenyl (23): As described in the preceding paragraph, starting from biphenyl **15** (1.5 g, 5.0 mmol) afforded colorless needles of **23**; yield: 1.69 g (81%).

6-Fluoro-2,2′-bis(dicyclohexylphosphino)biphenyl (24):[29] Biphenyl **11** (1.6 g, 5.0 mmol) was added to a solution of butyllithium (10 mmol) in hexanes (6.3 mL) and tetrahydrofuran (20 mL) at −75°C. After 15 min at −75°C, a solution of chlorodicyclohexylphosphine (2.0 mL, 2.0 g, 10 mmol) in tetrahydrofuran (10 mL) was added to the reaction mixture. Evaporation of the solvent followed by column chromatography on silica gel (100 mL) using cyclohexane as eluent gave a colorless oil. Crystallization from ethyl acetate/hexanes (1:5) afforded colorless needles; yield: 2.23 g (79%).

Dicyclohexyl-(4,5,2′,6′-tetramethoxybiphenyl-2-yl)phosphine (25): At −78°C, *tert*-butyllithium (4.0 mmol) in pentane (2.3 mL) was added dropwise to a solution of 2-bromo-4,5,2′,6′-tetramethoxybiphenyl (**20**, 2.0 mmol, 0.7 g) in tetrahydrofuran (10 mL). After 1 h, a solution of chlorodicyclohexylphosphine (2.0 mol, 0.5 g, 0.5 mL) in toluene (2.0 mL) was added dropwise. One hour later, the mixture was allowed to reach 25°C and was filtered on silica gel with diethyl ether as eluent. The organic layer was evaporated and the crude product was purified by chromatography on silica gel which afforded the monophosphine **25** as a white solid; yield: 0.07 g (7%).

Supporting Information

For the above procedures with full product characterization, please refer to the Supporting Information.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Acknowledgements

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grant 20–100–332–02), the Bundesamt für Bildung und Wissenschaft, Bern (grant C02.0060 linked to the COST-D24 project WG0006–02) and the Bundesamt für Berufsbildung und Technologie, Bern, in the framework of a KTI project (contract 5474.1 KTS). We are grateful to the CNRS and Ministère de la Recherche. F.R.L. is much indebted to Prof. M. Schlosser, Lausanne, for generous support and precious advice.

References

[1] K. B. G. Torssell, *Natural Product Chemistry*, Taylor & Francis, New York, **1997**.
[2] T. Okuda, T. Yoshida, T. Hatano, in: *Prog. Chem. Org. Nat. Prod.,* Vol. 66, (Eds.: W. Herz, G. W. Kirby, R. E. Moore, W. Steglich, C. Tamm), Springer, Wien, **1995**, p 1.
[3] G. Bringmann, F. Pokorny, in: *The Alkaloids,* Vol. 46, (Ed.: G. A. Cordell), Academic, New York, **1995**, p 127.
[4] S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, R. F. Brian, *J. Am. Chem. Soc.* **1973**, *95*, 1335.
[5] K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem. Int. Ed.* **1999**, *38*, 2097.
[6] D. H. Williams, B. Bardsley, *Angew. Chem. Int. Ed.* **1999**, *38*, 1173.
[7] P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297.
[8] C. Rosini, L. Franzini, A. Raffaelli, P. Salvadori, *Synthesis* **1992**, 503.
[9] L. Pu, *Chem. Rev.* **2004**, *104*, 1687.
[10] K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369.
[11] K. Mikami, K. Aikawa, Y. Yusa, J. J. Jodry, M. Yamanaka, *Synlett* **2002**, 1561.
[12] R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.
[13] R. Schmid, J. Foricher, M. Cereghetti, P. Schönholzer, *Helv. Chim. Acta* **1991**, *74*, 370.
[14] J. W. Goodby, N. A. Clark, S. T. Laggerwall, *Ferroelectric Liquid Crystals: Principles, Properties and Applications*, Gordon and Breach, Philadelphia, **1991**.
[15] P. J. Collings, M. Hird, *Introduction to Liquid Crystals Chemistry and Physics*, Taylor and Francis, London, **1997**.
[16] A. A. Patchett, R. P. Nargund, in: *Annu. Rep. Med. Chem. (Section IV)*, Vol. 35, (Ed.: G. L. Trainor), Academic Press, New York, **2000**, p 289.
[17] F. Leroux, *Curr. Med. Chem.* **2005**, *12*, 1623.
[18] F. Leroux, *ChemBioChem.* **2004**, *5*, 644.
[19] F. Leroux, T. U. Hutschenreuter, C. Charriere, R. Scopelliti, R. W. Hartmann, *Helv. Chim. Acta* **2003**, *86*, 2671.
[20] E. Baston, F. R. Leroux, *Recent Pat. Anti-Cancer Drug Discovery* **2007**, *2*, 31.
[21] F. Diederich, P. J. Stang, (Eds.), *Metal-catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.
[22] F. R. Leroux, R. Simon, N. Nicod, *Lett. Org. Chem.* **2006**, *3*, 948.
[23] M. Schlosser, *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[24] F. Leroux, M. Schlosser, E. Zohar, I. Marek, in: *Chemistry of Organolithium Compounds*, Vol. 1, (Ed.: Z. Rappoport), Wiley, Chichester, **2004**, p 435.
[25] M. Schlosser, in: *Organometallics in Synthesis: A Manual*, (Ed.: M. Schlosser), 2nd edn., Wiley, Chichester, **2002**, pp 1–352.
[26] F. Leroux, N. Nicod, L. Bonnafoux, B. Quissac, F. Colobert, *Lett. Org. Chem.* **2006**, *3*, 165.
[27] H. Gilman, B. J. Gaj, *J. Org. Chem.* **1957**, *22*, 447.
[28] T. K. Dougherty, K. S. Y. Lau, F. L. Hedberg, *J. Org. Chem.* **1983**, *48*, 5273.
[29] F. Leroux, M. Schlosser, *Angew. Chem. Int. Ed.* **2002**, *41*, 4272.
[30] L. W. Jenneskens, J. C. Klamer, W. H. De Wolf, F. Bickelhaupt, *J. Chem. Soc., Chem. Commun.* **1984**, 733.
[31] H. Richtzenhain, *Ber. Dtsch. Chem. Ges.* **1944**, *77B*, 1.
[32] H. Richtzenhain, A. Miedreich, *Chem. Ber.* **1948**, *81*, 92.
[33] A. I. Meyers, E. D. Mihelich, *J. Am. Chem. Soc.* **1975**, *97*, 7383.
[34] R. A. Rossi, A. B. Pierini, A. B. Penenory, *Chem. Rev.* **2003**, *103*, 71.
[35] J.-M. Becht, A. Gissot, A. Wagner, C. Mioskowski, *Chem. Eur. J.* **2003**, *9*, 3209.
[36] J.-M. Becht, S. Ngouela, A. Wagner, C. Mioskowski, *Tetrahedron* **2004**, *60*, 6853.
[37] L. Friedman, J. F. Chlebowski, *J. Am. Chem. Soc.* **1969**, *91*, 4864.
[38] For example: A. I. Meyers, P. D. Pansegrau, *Tetrahedron Lett.* **1983**, *24*, 4935.
[39] a) R. Maggi, M. Schlosser, *J. Org. Chem.* **1996**, *61*, 5430; b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; c) H. W. Gschwend, H. R. Rodriguez, in: *Organic Reactions*, Vol. 26, (Ed.: W. G. Dauben), Robert E. Krieger Publishing Company, Malabar, FL, **1979**, p 1; d) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
[40] F. Leroux, H. Mettler, *Adv. Synth. Catal.* **2007**, *349*, 323.
[41] F. Leroux, H. Mettler, *Synlett* **2006**, 766.
[42] O. Desponds, M. Schlosser, *J. Organomet. Chem.* **1996**, *507*, 257.
[43] K. Ziegler, F. Crossmann, H. Kleiner, O. Schafer, *Liebigs Ann. Chem.* **1929**, *473*, 1.
[44] H. Metzger, E. Müller, in: *Houben-Weyl: Methoden der organischen Chemie,* Vol. 1/2, (Ed.: E. Müller), Thieme, Stuttgart, **1959**, p 337.
[45] T. Sato, S. Shimada, K. Hata, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2484.
[46] M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, Y. Kondo, *J. Am. Chem. Soc.* **2002**, *124*, 8514.
[47] D. A. Lanfranchi, G. Hanquet, *J. Org. Chem.* **2006**, *71*, 4854.
[48] J. Schmid, G. Ladner, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 4402.
[49] T. Wenderski, K. M. Light, D. Ogrin, S. G. Bott, C. J. Harlan, *Tetrahedron Lett.* **2004**, *45*, 6851.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim